REMARKS

1. STATUS OF THE SPECIFICATION

The Specification has been amended to more accurately reflect government support.

2. STATUS OF THE CLAIMS

Claims 25-40 are pending in the application.

3. INFORMATION DISCLOSURE STATEMENT

The Examiner stated that the Information Disclosure Statement that was previously filed on 3/20/08 failed to comply with 37 CFR 1.98(a)(1), and that it "has been placed in the application file, but the information referred to therein has not been considered."[1] Applicants enclose a "Supplemental Information Disclosure Statement," references, and form PTO-1449 in compliance with 37 CFR §1.98(a)(1), and respectfully request consideration thereof.

4. REJECTION OF CLAIMS 25-40 UNDER 35 U.S.C. § 103(a)

Claims 25-40 continue to be rejected under 35 U.S.C. § 103(a)[2] for alleged obviousness over Kim *et al.* (2000)[3] in view of Kim *et al.* (1997),[4] Srivastava *et al.*,[5] and Mixson.[6] Applicants respectfully traverse. The Examiner is respectfully reminded that the U.S. Supreme Court has affirmed that a claimed combination is non-obviousness where there is a teaching away by the prior art. It said

> "... when the prior art **teaches away** from combining certain known elements, discovery of a successful means to combining them is more likely to be nonobvious."[7]

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1 Office Action, page 2, 4th paragraph.
2 Office Action, page 3, 3rd paragraph.
3 Kim *et al.*, J. Biol. Chem. 275:33920-33928 (2002).
4 Kim *et al.*, Biochem. Biophys. Res. Comm. 232:469-473 (1997).
5 Srivastava *et al.*, Mol. Cell. Biol. 18:3509-3517(1998).
6 Mixson U.S. Patent No. 6,080,728 (1997).
7 *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007).

Also, a

> "*prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, **teaches away** from the **claimed invention**."[8]

Applicants discuss below objective rebuttal evidence by de Rooij *et al.*[9] (Tab 1) and Amano *et al.*[10] (Tab 2) that teaches away from the claimed invention.

The Examiner is respectfully reminded that the Federal Circuit[11] has held that when rebuttal evidence is provided (as is the case here) the Examiner is required to "**start over**," reviewing the submitted facts against facts that were previously used by the Examiner to support the rejection:

> "If rebuttal evidence of adequate weight is produced, the holding of *prima facie* obviousness, being but a legal inference from previously uncontradicted evidence, is dissipated. Regardless of whether the *prima facie* case could have been characterized as strong or weak, the examiner must consider all of the evidence anew. The process is as stated in *In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976):
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> "When *prima facie* obviousness is established and evidence is submitted in rebuttal, the decision-maker must **start over**.... An earlier decision should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability. Analytical fixation on an earlier decision can tend to provide that decision with an undeservedly broadened umbrella effect. *Prima facie* obviousness is a legal conclusion, not a fact. Facts

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8 MPEP 2144.05 III, citing In re Geisler, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). See also, MPEP 2141.02 and 2145.

9 de Rooij *et al.*, "Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP," Nature 396:474-477 (1998).

10 Amano *et al.*, "Adenylate cyclase / protein kinase A signaling pathway enhances angiogenesis through induction of vascular endothelial growth factor *in vivo*," Jpn. J. Pharmacol. 87:181-188 (2001).

11 *In re Piaseki*, 745 Fed. 2d 1468 (Fed. Cir. 1984).

> established by rebuttal evidence must be evaluated along **with** the facts on which the earlier conclusion was reached, **not against** the conclusion itself....
> [A] final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by any earlier conclusion reached . . . earlier . . . upon a different record."[12]

Further, and prior to discussion of the particular facts in this case, the Examiner is respectfully reminded that the Federal Circuit has held that all differences, even if improperly characterized as minor differences, from the prior art must be considered. It said

> "Whether the changes from the prior art are 'minor,' . . . the changes must be evaluated in terms of the whole invention . . . "[13]

Applicants note that the "claimed invention" recites a particular molecule (i.e., "protein kinase A (PKA) catalytic subunit"), a particular cell type (*i.e.*, "endothelial cells" of Claims 25-32), and particular phenomena (i.e., "angiogenesis" of Claims 25-32, and "apoptosis" of Claims 33-40). Thus, a proper analysis of non-obviousness must consider the prior art's teachings with respect to these particular elements. In view of this, Applicants' following discussion addresses the claims into two groups: Claims 25-32 that recite the elements of "PKA", "endothelial cells" and "angiogenesis," and Claims 33-40 that recite the elements of "PKA" and "apoptosis."

A. <u>The Prior Art Teaches Away from Claims 25-32</u>

Amano *et al.* teaches that their data "demonstrated that [the AC/PKA] signaling pathway certainly contributed to angiogenesis."[14]

The above teaching that PKA **increases angiogenesis** is **<u>diametrically opposite</u>** from independent Claim 25, which teaches that expression of the PKA catalytic subunit **reduces**

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12 Emphasis added.

13 *Northern Telecom, Inc. v. Datapoint Corporation*, 908 F.2d 931, 934-35,15 USPQ2d 1321, 1323-24 (Fed. Cir. 1990).

14 Amano *et al.*, page 187, 2nd column, first paragraph.

angiogenesis.

Indeed, Amano *et al.*'s above statement was factually based on their *in vivo* data in a rat model that showed that

> "**Angiogenesis . . . was suppressed by . . . H-89, and inhibitor for PKA**,"[15] "the topical administration of **H-89, an inhibitor for PKA**, also **reduced** the intensity of this naturally occurring **angiogenesis**. The **activation of the AC/PKA** signaling pathway may have the function of **enhancing** naturally occurring **angiogenesis** in this model. This hypothesis was further supported by the result observed in angiogenesis enhanced by topical injection of forskolin or amrinone. **H-89 a**nd SQ22,536 **inhibited** the **angiogenesis** stimulated with forskolin or amrinone (Fig. 4.)"[16]

Furthermore, Applicants note that the *in vivo* model of angiogenesis used by Amano *et al.* "was reliable for quantifying angiogenesis."[17]

In addition, in reviewing the state of the prior art as a whole, Amano *et al.* commented that the prior art collectively taught that

> "it is plausible that one of the major signaling pathways for **facilitating angiogenesis** may be a **cAMP-dependent** one."[18]

Importantly, Amano *et al.* was published in 2001, which is after the publication date in 2000 of the primary reference Kim *et al.* In other words, Amano *et al.*'s objective assessment of the state of the prior art **as a whole** (including a presumed knowledge of the prior Kim *et al.* (2000) and Kim *et al.* (1997)), was that PKA **increased**, rather than **decreased**, angiogenesis.

From the above, both the state of the art and Amano *et al.*'s specific data regarding angiogenesis teach one of skill in the art to proceed in a direction that is **diametrically opposite**

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15 (Emphasis added) Amano *et al.*, Abstract,
16 (Emphasis added) Amano *et al.*, page 183, 2nd column, 3rd paragraph, and Fig. 3.
17 Amano *et al.*, page 185, 2nd column.
18 (Emphasis added) Amano *et al.*, page 181, 1st and 2nd columns.

from the direction undertaken by the inventors to arrive at the claimed invention. Proceeding **contrary to the accepted wisdom** is "strong evidence of unobviousness."[19]

Applicants also incorporate the prior arguments made in Dr. Varner's Declaration with respect to the teaching away by de Rooij *et al.* In particular, while Kim *et al.* (2000) used forskolin and dibuteryl cAMP to inhibit angiogenesis, de Rooij *et al.* teaches that both forskolin and cAMP were known to act via more than one pathway. For example, de Rooij *et al.* disclosed

> "that activation of Rap1 by forskolin and cAMP **occurs independently of protein kinase A.**"[20]

De Rooij *et al.* further demonstrated that instead of activating protein kinase A, cAMP binds to Epac (exchange protein directly activated by cAMP), which in turn "induces the GEF activity of Epac towards Rap1."[21] De Rooij *et al.* also said "that **not all cAMP-induced effects are mediated by either PKA** or cyclic-nucleotide-gated channels, the only previously known cAMP-target proteins. Several reports have suggested the existence of such pathways . . ."[22]

Thus, there was **uncertainty** about whether Kim *et al.*'s anti-angiogenic effects of forskolin and cAMP were the result of activation of Epac, of PKA, or other pathways that were referred to by De Rooij *et al.* The disclosure in Kim *et al.* (2000) **did not resolve this uncertainty** because Kim *et al.*'s finding were **contradicted** by the later-published Amano *et al.* that used a quantitative *in vivo* assay to show increased angiogenesis, instead of Kim *et al.*'s reduced angiogenesis, by a PKA signaling pathway. Indeed, this unpredictability was not resolved until after the inventors obtained exemplary data that was first disclosed in the instant application, and that showed that

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19 *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 1552, 220 USPQ 303, 312 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *United States v. Adams*, 383 U.S 39, 148 USPQ 479 (1966); *In re Hedges*, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986).

20 de Rooij *et al.*, Abstract.

21 de Rooij *et al.*, Abstract.

22 de Rooij *et al.*, page 476, 2nd column, 3rd paragraph.

"activation of PKA by cAMP ($P<0.0003$, Figure 23*c*) or by **expression of the catalytic subunit of PKA** in the CAM ($P=0.0005$, Figure 23*d*) potently **inhibits angiogenesis**."[23]

Applicants also incorporate Dr. Varner's prior Declaration, which establishes solid reasons why one of skill in the art would not have combined Kim *et al.* (2000) with the teachings of the remaining references, namely that (a) Kim *et al.* (1997) relates to a **different cell type** (neuroblastoma cells versus "endothelial cells" that participate in the recited angiogenesis) and **different phenomenon** (growth versus the recited angiogenesis), (b) Mixson relates to a **different phenomenon** (tumor growth versus the recited angiogenesis), and (c) Srivastava *et al.* refers to a **different phenomenon** (apoptosis versus the recited angiogenesis).

Applicants comment as follows on the Examiner's response to the prior arguments. The examiner argued that "Firstly, the examiner notes that Applicants consider each cited references in total isolation one from the others; and this is improper."[24] However, this mischaracterizes Applicants' arguments that directed the Examiner's attention to the particular elements of the claims, and to the need under the law for the references to teach combining the elements in the manner claimed.

The Examiner also argued "Secondly as already stated above that the primary Kim *et al* (2000) reference clearly disclosed that the suppression of angiogenesis *in vivo* is mediated by PKA and suggested explicitly the potential use of PKA agonists in the treatment of angiogenic diseases, including cancer and arthritis."[25] However, as discussed above, Kim *et al.*'s finding were **contradicted** by the later-published Amano *et al.* that used a quantitative *in vivo* assay to show increased angiogenesis, instead of Kim *et al.*'s reduced angiogenesis, by a PKA signaling pathway.

The Examiner additionally argued "Thirdly, Mixson taught successfully and clearly a method for inhibiting tumor growth in a subject bearing a tumor comprising injection of DNA encoding at least one anti-angiogenic protein or peptide specifically targeting the tumor and/or tumor vasculature (made up of endothelial cells); and all of the tumors are very dependent on

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[23] Specification, Example 34, beginning on page 152.
[24] Office Action, page 8, 3rd paragraph.
[25] Office Action, page 8, last full paragraph, citing Kim *et al.* (2000) "page 33927, col. 2, last paragraph continues to first two lines in col. 1 of page 33928."

blood supply (requiring angiogenesis) to sustain their growth."[26] However, Mixson *et al.* discloses **generic methods** for reducing angiogenesis by expressing genes that encode the anti-angiogenic proteins Thrombospondin I ("TSPI"), it angiogenic fragment TSPf, angiostatin, and laminin. However, Mixson does not mention using the recited PKA catalytic subunit, and the availability of generic methods alone is insufficient to establish obviousness. Indeed, the role of expression of PKA in reducing angiogenesis was not fully established until the inventors' disclosure in the instant application.

The Examiner further argued that "Kim *et al* (1997) already taught that overexpression of a protein kinase A catalytic subunit mediated by a recombinant retroviral vector in SD-N-SH human neuroblastoma cells resulted in a 3-fold increased PKA activity in the absence of cAMP, increase type II protein kinase A activity and cellular growth inhibition."[27] However, this disclosure relates to neuroblastoma cells, not the recited "**endothelial cells**", and to cell growth, not the recited "**angiogenesis**." There is no factual evidence that validates the propriety of extrapolating between **both** the different cells and different phenomenon of Kim *et al.* (1997) and those recited in the claims.

In view of the above, Claims 25-32 are nonobvious.

B. Claims 33-40 Are Non-Obvious

Applicants incorporate their prior arguments and Dr. Varner's prior Declaration, which provided a solid basis for why one of skill in the art would not have combined the references to arrive at the claims, namely that (a) Kim *et al.* (2000) relates to different phenomena (angiogenesis and cell migration versus the recited apoptosis), (b) Kim *et al.* (1997) relates to a different phenomenon (growth versus the recited apoptosis), (c) Mixson relates to a different phenomenon (tumor growth versus the recited apoptosis), and (d) Srivastava *et al.*'s effects on apoptosis could have occurred via PKA-independent pathways that were know to exist at the time of the invention, including via Epac and others.[28] In addition, Srivastava *et al.*'s data relates to determining the effect of PKA activators and inhibitors of protein kinase A on apoptosis. This is different from the claimed invention that recites increasing apoptosis by "expressing" a

[26] Office Action, paragraph bridging pages 8-9, citing Mixson "col. 10, lines 15-19; col. 4, lines 47-54 and example 1."
[27] Office Action, page 9, 1st paragraph.
[28] De Rooij *et al.*, Abstract.

nucleotide sequence that encodes a PKA catalytic subunit. In other words, even if the effect of Srivastava *et al.*'s PKA activators and PKA inhibitors was to reduce apoptosis and to increase apoptosis, respectively, this does not necessarily provide a reasonable expectation of success that using a different methodology, *i.e.*, "expressing" PKA, will increase apoptosis. Establishing a *prima facie* case of obviousness requires the Examiner to provide objective evidence in support of this.

The Examiner argued that "Srivastava *et al* also taught that activation of cAMP-dependent protein kinase A by Paclitaxel, forskolin or okadaic acid induced Bcl2 hyperphosphorylation and apoptosis in cancer cells which were blocked by the PKA inhibitor Rp diastereomers of cAMP."[29] The Examiner also argued that "Fourthly, there is no factual evidence provided by Applicants [that] indicated or suggested that the PKA inhibitor Rp diastereomers of cAMP used by Srivastava *et al* is non-specific and that it can act on pathways other than via protein kinase A. Moreover, Srivastava *et al* clearly concluded that protein kinase A is involved in the induction of Bcl2 hyperphosphorylation and induction of apoptosis in a peer-reviewed article (see at least the abstract)."[30]

However, as discussed above, it is the Examiner's burden to provide **objective evidence** showing that reducing apoptosis and increasing apoptosis by PKA activators and PKA inhibitors, respectively, provides a reasonable expectation of success that using the different methodology of "**expressing**" PKA will increase **apoptosis**. Indeed, this was not firmly established until after the inventors obtained the exemplary data that was first disclosed in the instant application, and that showed that

> "**Expression of the PKA catalytic subunit** in bFGF-stimulated CAMs or exposure of CAMs to cAMP also **induces endothelial cell apoptosis** *in vivo* (Figure 23*f*)."[31]

In the absence of the above-discussed objective evidence, a *prima facie* case of obviousness is not established.

Based on the above, Claims 33-40 are nonobvious.

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29 Office Action, page 9, 1st paragraph.
30 Office Action, page 9, last paragraph.
31 Specification, Example 34, beginning on page 152.

Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 25-40 under 35 U.S.C. § 103(a) over Kim *et al.* (2000) in view of Kim *et al.* (1997), Srivastava *et al.*, and Mixson.

CONCLUSION

Applicants respectfully request reconsideration of the application. Applicants believe the claims are in condition for allowance. Should the Examiner believe a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned.

Dated: December 15, 2008

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